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Urinary metabotypes in patients with chronic hepatitis C virus infection as revealed by nuclear magnetic resonance-based metabolomics

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Background: Metabolomics has the potential to identify non-invasive biomarkers of liver pathology. In the present study, a metabolomic approach was employed to characterize the urinary metabolome in patients with chronic hepatitis C virus (HCV) infection and different grades of liver fibrosis.

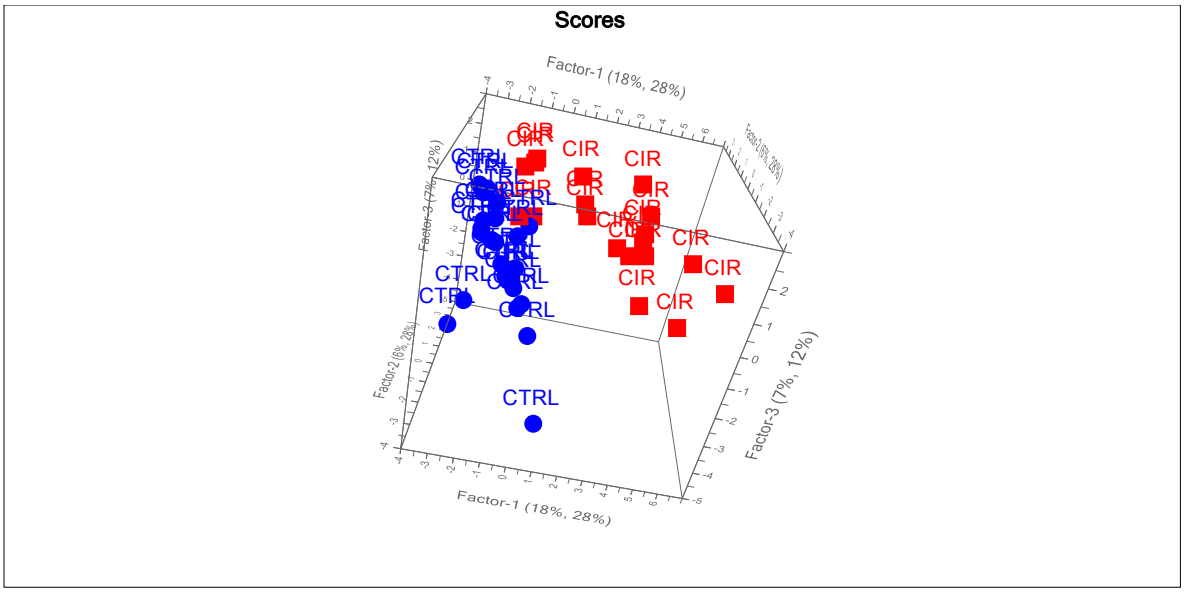
Material/methods: 43 individuals, 24 controls and 19 pts with HCV and liver fibrosis were compared. Diabetics were excluded. The urine were collected before starting anti-HCV therapy. Fibrosis was assessed by transient elastography (Fibroscan).
Metabolomics was performed on fast morning urines by using ^{1}H Nuclear Magnetic Resonance (NMR) Spectroscopy. Partial least square (PLS) discriminant analysis was applied

to characterize the difference between HCV patients with different severity of fibrosis and healthy subjects.

Results: 43 individuals, 24 controls (15 M/9 F; age 59.3 ± 9.0) and 19 HCV pts (12 M/7 F; age 59.6 ± 9.6; BMI 24.6 ± 3.4, ALT 76.7 ± 37.5 U/L; e-GFR 95.6 ± 8.9 mL/min/1.73m²; liver stiffness 18.7 ± 5.9) were enrolled. 43 ^{1}H nmr spectra were analyzed and 49 metabolites were quantified. The PLS2 analysis was applied to separate the contribution of gender-linked metabolic variability from that generated by the HCV and fibrosis. The PLS modeling showed a different metabolic profile characterized by significant changes in seven urinary metabolite levels for HCV/fibrosis (R^2=0.86 and Q^2=0.56) (Figure). The contribution of the gender-linked metabolic changes in healthy and HCV pts could be separated and quantified. In order to evaluate the effect of fibrosis severity on metabolic profiling, we performed the analysis only on male subjects. The PLS modeling showed a significant metabolic profile characterized by six metabolite level changes (R^2=0.83 and Q^2=0.47). Four metabolites among these were present in the previous modeling, showing to be dependent on the liver disease and to vary in relation to fibrosis severity. The urinary metabolic profile of HCV/fibrosis was described by higher levels of pseudouridine, hypoxanthine and methylnicotinamide and lower levels of glycine independently on the gender.

Conclusions: These preliminary data defined a urinary metabotype associated to HCV infection and liver fibrosis. The latent variables scores co-variated with liver stiffness values, suggesting that pseudo-uridine, hypoxanthine, methyl-nicotinamide and glycine are potential non-invasive, metabolic biomarkers of disease and are not influenced by gender.

Figure: 3D Latent Variable score plot of HCV patients (CIR) and controls (CTRL)


Scores
Factor-1 (18%, 28%)
Factor-3 (7%, 12%)
Factor-2 (6%, 28%)
CIR
CTRL